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Ocular symptoms and signs in patients with ectodermal dysplasia syndromes

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Abstract *Purpose:* The ectodermal dysplasia syndromes are underestimated although precise inclusion criteria have been formulated. The purpose is to establish easily detectable ophthalmologic symptoms and signs as reliable criteria for ectodermal dysplasia syndromes. *Methods:* Thirty-six patients with confirmed ectodermal dysplasia syndromes were included in an observational case series: hypohidrotic ectodermal dysplasia (30), EEC syndrome (3), AEC syndrome (2), Gorlin–Goltz syndrome (1). Each patient was examined ophthalmologically. The principal outcome measures were ocular symptoms and signs in patients with different ectodermal dysplasia syndromes of varying severity. *Methods:* Some 94.4% of the patients suffered from dry eye symptoms. Reduction of eyebrows was seen in 94.4%; the lashes were altered in 91.6%. Changes of the meibomian glands were detected in 95.45%. Corneal changes such as pannus occurred later in life. *Conclusions:* Alterations of the meibomian glands, which were detected by meibomianoscopy, are the most reliable ocular sign of ectodermal dysplasia syndromes.

Introduction

The ectodermal dysplasia syndromes are a group of genetic disorders that are identified by the absence or deficient function of at least two derivatives of the ectoderm such as teeth, hair, nails and sweat glands. The possible pathologies include dental anomalies, trichodyplasias, onychodysplasias and dyshidrosis [1].

The prevalence of this group of syndromes can only be estimated. The overall prevalence seems to be in the order of 100 per 1 million of population. The Birth Defects Encyclopedia indicates seven patients with ectodermal dysplasia in 10,000 births.

More than 150 different ectodermal dysplasia syndromes are registered. The most prominent forms [2] among these are:

- Hypohidrotic ectodermal dysplasia (HED) (McKusick no. 12949)
- Ectrodactyly–ectodermal dysplasia–clefting syndrome (EEC syndrome) (McKusick no. 12990)
- Hidrotic ectodermal dysplasia (Clouston syndrome) (McKusick no. 12950)
- Ankyloblepharon–ectodermal dysplasia–clefting syndrome (AEC syndrome, Hay–Wells syndrome) (McKusick no. 106260)
- Incontinentia pigmenti (McKusick no. 308300)
- Anhidrotic ectodermal dysplasia–clefting syndrome (Rapp–Hodgkin syndrome) (McKusick no. 12940)
- Trichodentoosseous syndrome (McKusick no. 190320)
- Tooth-and-nail syndrome (Witkop syndrome) (McKusick no. 189500)

The four most frequent syndromes among these are HED, EEC, AEC and hidrotic ectodermal dysplasia. This is also emphasised by the questionnaire results of the American self-help group for ectodermal dysplasia (NFED) [3].

Patients with ectodermal dysplasia syndromes suffer above all from dental anomalies, dry skin and dyshidrosis. The ocular anomalies are less frequently observed [4]. Disorders of the tear film and deformities of the meibomian glands are described for the EEC syndrome [5].

Alterations of the eyebrows and lashes are mentioned in combination with several ectodermal dysplasia syndromes. Anomalies of the lacrimal system are seen in patients with EEC syndrome [6]. A patient with anhidrotic ectodermal dysplasia has been reported to develop corneal opacifications [7].

We were interested to find out whether the meibomian glands are changed in the ectodermal dysplasia syndromes. Meibomian gland deformities have so far only been described in patients with EEC syndrome [8, 9]. There is evidence that, based on the similar pathology, the other ectodermal dysplasias should also be combined with meibomian gland alterations. Knowledge about that might yield information useful in developing prophylactic therapy for lipid disorders of the tear film of patients with hyperevaporative dry eye [10]. Moreover, it would give a better understanding of what happens to the cornea when it is covered by a defective lipid film over a long period.

Methods

Thirty-six patients with ectodermal dysplasia syndromes were included in the study. The presence of at least two deformities in ectodermal systems was an inclusion criterion. Furthermore, most patients included had undergone genetic counselling as well as genetic and clinical confirmation of the diagnosis. Others had had sweat gland examination to demonstrate their hypohidrosis.

The patients of this observational case series were recruited from the German self- help group for ectodermal dysplasia syndromes between May 2001 and May 2002. Patients were selected prospectively and consecutively. Informed consent was signed prior to the ophthalmologic examination. The approval of the local ethics committee was obtained.

One patient was recruited from Ludwigshafen Eye Hospital, and two patients came from Homburg University Eye Hospital.

The patient's history was taken in all cases. The ocular symptoms relating to the tear film were registered, alterations of eyebrows and lashes documented.

Meibomianoscopy [11] was performed with a modified cold-light lamp from a vitrectomy system (Millennium, Bausch & Lomb) in patients over the age of 8 years. The anterior segment examination was performed using a slit lamp; children under the age of 5 years were examined using a hand-held slit lamp.

The photographic documentation of those patients who agreed to it included images of the face, the teeth, the hands and the eyelids. Masking of the patients was performed using continuous numbering. The study was not designed on a follow-up basis. The sample size resulted from the available patients, who were examined during the annual meetings of the self-help group. Separate examinations were performed on the three clinical patients. All data were collected prospectively during an interview and an ophthalmologic examination. The clinical signs were documented as "present" or "absent".

Results

Thirty-six patients were included in the study. Their age was between 1 and 72 years with a mean of 21.9 years. Among these were 22 female and 14 male patients. They came from Germany, Austria and Switzerland. Patients living in cities with more than 1,000,000 inhabitants were slightly over-represented.

Thirty patients of this study suffered from HED. There were three patients with EEC syndrome, two patients with AEC syndrome and one patient with Gorlin–Goltz syndrome. This is one of the rare ectodermal dysplasia syndromes, with additional mesodermal changes.

Twenty-two patients (94.4%) suffered from ocular complaints related to the ocular surface. They reported tearing, burning, photophobia, redness and recurrent inflammations of the lids.

Diminution of the eyebrows was seen in 34 patients (94.4%), whereas alteration of the lashes was detected in 91.6%.

Transillumination of the meibomian glands was performed on 22 patients and revealed alterations of the meibomian glands in 21 of them (95.45%). These alterations included partial loss of the glands, coarsening of the acini and complete absence of meibomian glands. There was always a symmetrical alteration in all the examined lids.

During the slit-lamp examination a pannus corneae was detected in seven patients (19.4%). Patients with pannus corneae were older than the study group as a whole. Their mean age was 29.7 years.

Case history 1

A 20-year-old woman presented with dry, thin skin; she had coarse hair and complained of irregular cracking nails (Fig. 1). Due to delayed tearing, genetic counselling had been carried out at the age of 1.5 years. The diagnosis of HED was based on genetic results as well as clinical findings. Based on her family history a spontaneous mutation was supposed. She at present has pronounced teeth deformities. The skin showed clearly defined areas of normal and reduced sweating.

Ophthalmologically, she had laterally reduced eyebrows and lashes, the position of which is symmetrical. She did not complain of ocular symptoms. Her visual acuity was 1.0 on both eyes. She presented with a clear cornea and an intact limbal area. The break-up time (BUT) was 10/11 s. On meibomianoscopy she showed distinct areas of irregular glands. Their acini were coarse and exhibited little branching.

Despite the reduced BUT the patient did not complain of dry-eye symptoms. We nevertheless recommended lipid-containing eye drops on a carbomer basis, because the meibomian glands are altered and the lipid layer of the tear film is changed.

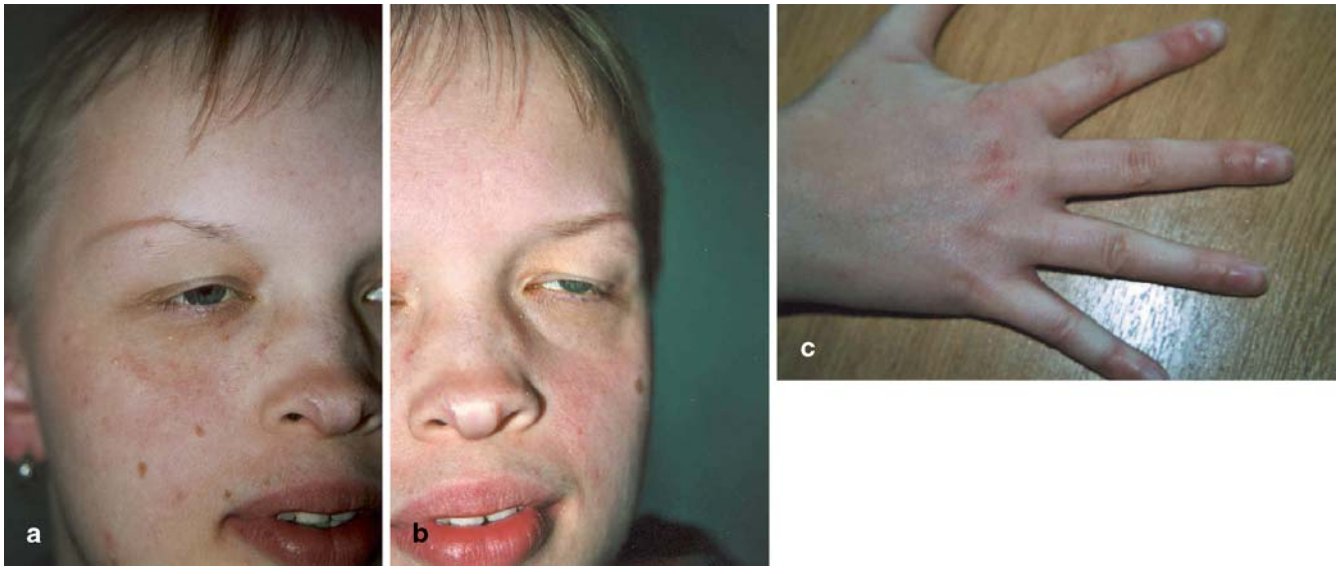

Fig. 1a–c A 20-year-old woman with hypohidrotic ectodermal dysplasia. The saddle-backed nose is typical, as is the short and sparse hair. Note the papular skin of the face and the lids. The fingers present with hypertrophy of the lateral and posterior surface of the phalangeal joints

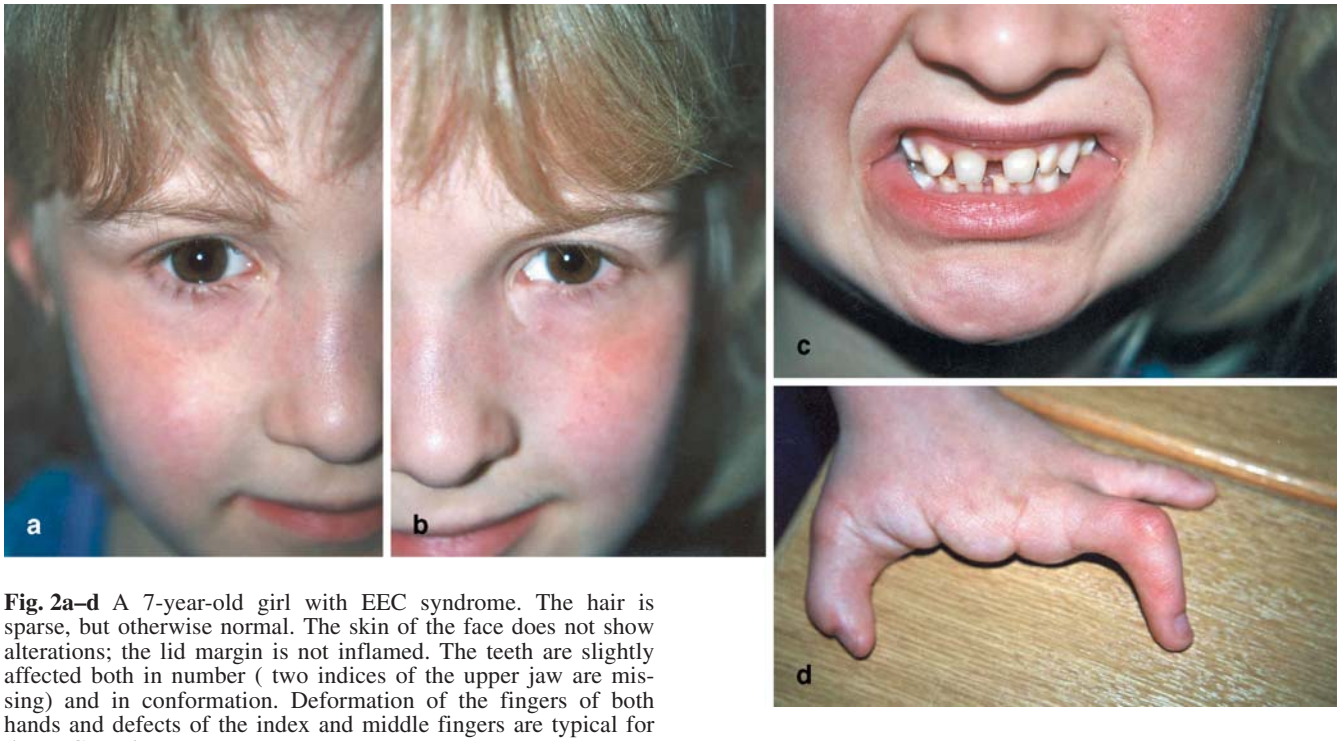

Fig. 2a–d A 7-year-old girl with EEC syndrome. The hair is sparse, but otherwise normal. The skin of the face does not show alterations; the lid margin is not inflamed. The teeth are slightly affected both in number (two indices of the upper jaw are missing) and in conformation. Deformation of the fingers of both hands and defects of the index and middle fingers are typical for the EEC syndrome

Case history 2

A 7-year-old girl presented with thin, though otherwise normal hair. Her skin was dry and she suffered from neurodermitis (Fig. 2). Because of a bilateral deformity of the index and the middle fingers a genetic examination had been performed 5 days after her birth. The diagnosis "EEC syndrome" was stated. A spontaneous mutation seemed to be the most probable explanation for the occurrence of this syndrome. Later on, nail anomalies be-

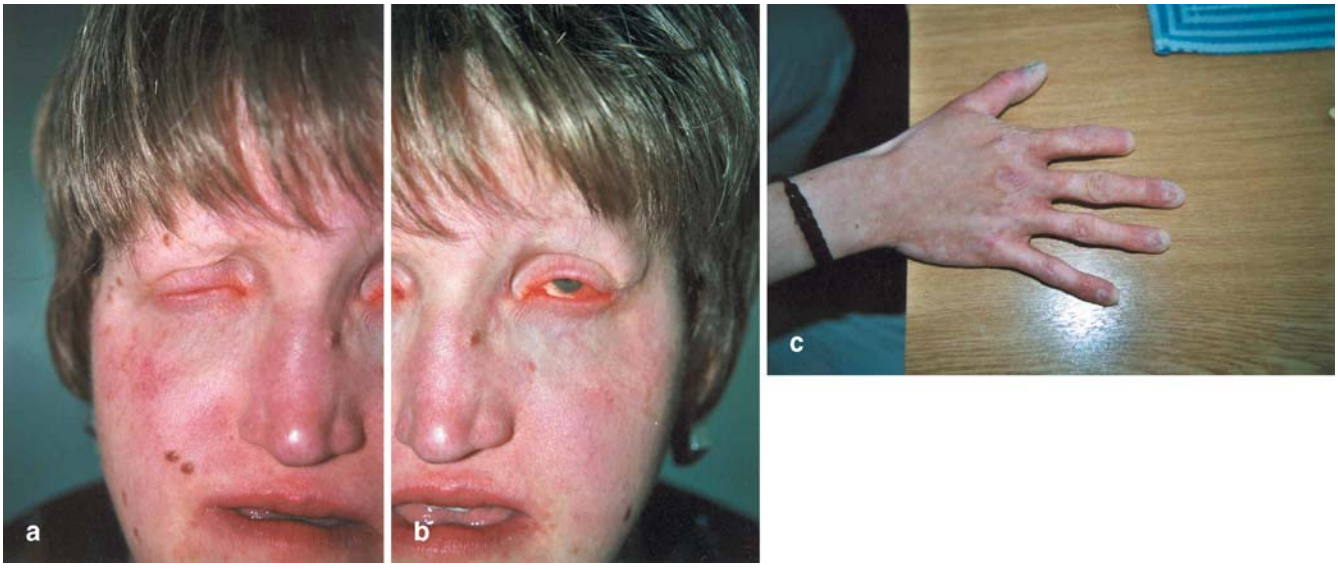

Fig. 3a–c A 35-year-old woman with AEC syndrome. Massive papular skin of the face and seborrhoeic blepharitis can be seen. Peri-oral redness is characteristic. Dryness of skin at the fingers leads to cracking and subsequent leukoplakia

came apparent, teeth defects appeared and recurrent bronchitis was difficult to treat. At present she has only few signs of hypohidrosis.

Ophthalmologically recurrent blepharitis was reported by the patient, but at the time of the examination her lid margin was normal. She had undergone three operations on the lacrimal excretory system. Eyebrows and lashes were only slightly reduced. No dry-eye symptoms were present; the cornea and the limbal region were normal. Neither meibomianoscopy nor tear film testing could be performed due to her young age.

We recommended a blepharitis therapy only for the phases of clinical signs. Otherwise lid hygiene seemed to be sufficient.

Case history 3

A 35-year-old woman wearing a wig because of an almost complete alopecia presented with dry skin and multiple nail deformities (Fig. 3). A palatoschisis had been treated surgically in childhood. She had suffered recurrent middle ear infections as a child. At the age of 17 a genetic examination had been conducted, resulting in the diagnosis of AEC syndrome.

The patient had diminished eyebrows and lashes. Additionally, trichiasis had had to be treated operatively. The visual acuity was 0.6 in both eyes. Meibomianoscopy revealed absence of meibomian glands. Corneal opacifications with vascularisation were seen on both sides. The Schirmer test result was 4/5 mm. There was positive fluorescein and Rose Bengal staining.

We recommended regular tear substitutes with lipid-containing eye drops, with intermittent addition of non-preserved tear substitutes containing hyaluronic acid. For the night, ointment was added because of a partial lagophthalmos.

Discussion

The ectodermal dysplasia syndromes are a group of genetic disorders which are characterised by clinical alterations of ectodermal tissues. Despite the large number of about 150 individual syndromes, the entity of ectodermal dysplasia syndromes is well defined. The clinician faces the difficulty that every syndrome may vary tremendously between mild and severe forms (e.g. HED in female carriers compared with HED in male patients).

The ectodermal dysplasia syndromes are classified into two main subgroups: In one group, sweating is deficient. Here the absence of sweat glands coincides with varying degrees of tooth, hair and nail deformities [12]. In the other group sweating and the teeth are normal, but there are alterations of hair and nails. This classification goes back to the description of Goeckermann in 1920 [13], who found absent sweat glands, and Clouston in 1929 [14], who described the presence of sweat glands.

The division into hypohidrotic and anhidrotic ectodermal dysplasia is problematic. Usually patients with ectodermal dysplasia syndromes report distinct areas of the skin with normal sweat function and others with impaired sweat function. They normally can indicate some kind of sweat mapping especially for sensitive areas like the palm.

In fact, most patients with anhidrotic ectodermal dysplasia seem to be hypohidrotic in their clinical appear-

ance. There is a certain inaccuracy in naming them anhidrotic, which dates back to the classification of Weech in 1929 [15]. We classify the patients in our series as hypohidrotic in accordance with Felsher [16}.

The EEC syndrome is well defined with respect to the ocular signs. Mondino [8] found an absence of meibomian orifices at the upper and lower lid. He showed that histologically the meibomian glands were completely absent. The biomicroscopic absence of meibomian orifices was also reported by Koniszewski [4], but not confirmed by histologic series. In their literature review, the same authors found that 14 of 131 reported EEC patients had alterations of the meibomian orifices.

The appearance of the meibomian orifices does not imply any information about the whole gland. Even if the orifice is absent the meibomian gland can be completely normal. For clinical information full-thickness biopsies cannot be performed routinely. The technique of transillumination (meibomianoscopy) provides useful information. In contrast to histologic techniques all areas of the upper and lower lid can be inspected. The meibomianoscopy provides information about regularity, differentiation, size and number of the meibomian glands. We therefore chose this technique for our series.

Based on our clinical observations we were interested to know whether the meibomian gland alterations could also be found in other forms of ectodermal dysplasia. With respect to the ectodermal disorder this seemed likely. It would also give an explanation for the keratopathy that was observed in patients with HED by Wilson [7] and Koniszewski [4].

We demonstrated that all the patients examined by meibomianoscopy showed alterations of the meibomian glands. Minor clustering was detected besides a complete absence of glands. The changes could be seen in distinct areas of the lid or along the complete lid margin. In general, the changes were distributed symmetrically. Thus, the alteration of the meibomian gland is an elementary sign of the ocular involvement in ectodermal dysplasia syndromes. It ranks as an important clinical sign of the syndromes alongside the hypotrichia of lashes and eyebrows.

This sign seems to be important not only for the syndromes investigated in this series (HED, AEC, EEC, Gorlin–Goltz), but possibly for the remaining syndromes too. This remains to be tested. In our series we had different age groups. Alterations of the meibomian glands were seen in all our age groups, even in the younger patients. We could not perform meibomianoscopy for accurate lid margin examination in patients under the age of 8 years because of their lack of compliance.

Our patients with ectodermal dysplasia syndromes had ocular complaints in 94.4% of cases. These complaints (burning, foreign body sensation, tearing, photophobia) were, in most cases, not reported spontaneously but on questioning. This may be related to the apparent predominance of complaints in other areas, such as skin, hair and teeth, in childhood. Ocular symptoms seem to gain importance later in life. In the literature severe ocular symptoms are described for adult patients with ectodermal dysplasia by Mondino [8] and Koniszewski [4].

In our series corneal changes were seen in 19.4% of cases. The patients with corneal changes were older than the group as a whole (29.7 years compared with 21.9 years). We selected pannus corneae as criterion for relevant keratopathy. Our data indicate that corneal involvement occurs above all in adults. Despite the fact that younger patients report symptoms related to the ocular surface, the manifest alterations of the surface of the eye appear later in life. Occasionally, keratopathy is the most disabling sign of the ectodermal dysplasia syndrome.

There is evidence that keratopathy in ectodermal dysplasia syndromes is the result of an altered lipid layer of the tear film. It is, in fact, an indirect consequence of the meibomian gland alteration [7]. The age-dependent appearance of keratopathy would favour this hypothesis. Besides that, there are cases with an early onset of keratopathy. Some researchers (e.g. Baum [17]) think that corneal alterations are a primary sign of ectodermal dysplasia syndromes, starting with an epithelial insufficiency and ending with stromal scarring and vascularisation. It remains unclear why, in many cases, the corneal epithelium remains intact whereas the stroma, which is of non-ectodermal origin, shows opacifications. This calls for further research.

Although longitudinal studies are missing, there are hints that the ocular surface disease in ectodermal dysplasia syndromes is a progressive disease. One family was examined in 1970 by Wiegman and re-examined in 1985 by Mawhorter [5]; the progression of the disease could be documented. From our 36 patients' histories we can derive that the symptoms increase with age; the corneal changes appear later in life. Therefore, it seems reasonable to start prophylactic therapy as soon as symptoms are noticed. We recommend lipid-containing eyedrops on the basis of carbomer [18]. Whether systemic application of ω-3-fatty acids is useful remains to be tested [19]. Additionally, regular lid-hygiene either with swabs or cotton buds or with baby shampoo is useful to minimise recurrent infections of the lid margin. If corneal involvement without an epithelial defect has started, local steroids are required. In the case of epithelial defects short-term antibiotics are necessary instead of steroids, mostly combined with ointment.

The mode of inheritance varies from one syndrome to the other within the ectodermal dysplasia group. We investigated patients with four different syndromes in our series.

HED can be inherited in autosomal dominant, autosomal recessive or X-linked fashion. In our group 26 patients had been classified as having spontaneous mutations. Four patients were known carrier females with

very mild clinical signs. These four patients have an X-linked HED. Besides this genetic heterogeneity, an allelic heterogeneity may lead to variant clinical signs. Variable penetrance and expressivity also modify the clinical result. The gene localisation is Xq12-q13.

The EEC syndrome has an autosomal dominant mode of inheritance. Genetic heterogeneity has been postulated. It has a high penetrance of 95–98%; the expressivity varies. The existence of a gonadal mosaic seems at present the most probable explanation for the clinical signs. The gene localisation is reported by Qumsiyeh as the area between 7q11.2 and 7q21.3 [20]. A translocalisation to 9q12 has been shown by fluorescence in situ hybridisation [21]. One patient in our group was a sporadic case, while the other two patients were a father and his son.

The AEC syndrome has an autosomal dominant mode of inheritance. The gene localisation is not known. The patient in our group represented a spontaneous mutation.

Gorlin–Goltz syndrome has an X-chromosomal dominant mode of inheritance.

All the above-mentioned syndromes have an ectodermal disorder in common. They are said to be the results of deficient orchestration in organogenesis. This is the result of deficient regulatory proteins. One of these is ectodysplasin A. Tabby mice, which are characterised by a lack of ectodysplasin A, show the signs of HED. They are an animal model for this disease [22]. Interestingly, the intravenous application of epidermal growth factor partially rescues the phenotype of the sweat gland defect via a de novo synthesis of the glands [23]. The effect on the meibomian glands has not yet been researched.

Other orchestration proteins co-ordinating the organogenesis are the transmembrane proteins collagen XVII and plakophilin. Thus, we have an animal model for the disease at our disposal as well as the knowledge of three different regulatory proteins. This opens new avenues for therapeutic concepts. Apart from this genetic approach, therapy in ectodermal dysplasia syndromes is always a multidisciplinary task.

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